

## **REMARKS**

### ***Status of the Claims***

Upon entry of the present amendment, claims 1-25 will remain pending in the above-identified application, with claims 10-12 and 16-25 standing ready for further action on the merits, and remaining claims 1-9 and 13-15 being withdrawn from consideration based on an earlier restriction requirement of the Examiner.

Claims 10 and 11 have been amended and new claims 16-25 have been added.

Support for amended claims 10 and 11 can be found at paragraph [0036] bridging pages 9 and 10 of the present specification, particularly at lines 1 to 4 on page 10 of the specification.

Support for new claim 16 can be found at the paragraph [0023] on pages 5 and 6 of the present specification, and originally filed claim 2.

Support for new claim 17 can be found at the paragraph [0035] on page 9 of the present specification.

Support for new claim 18 can be found in Reference example 1 on page 12 and Reference example 2 on page 16 of the present specification.

Support for new claim 19 can be found in Example 1 on page 13 and Example 6 on page 17 of the present specification.

Support for new claims 20 and 21 can be found at the paragraph [0037] on page 10 of the present specification.

Support for new claims 22-24 can be found at the paragraph [0038] on page 10 of the present specification.

Support for new claim 25 can be found at the paragraph [0039] on page 10 of the present specification.

Accordingly, the present amendments to the claims do not introduce new matter into the application as originally filed. As such entry of the instant amendment and favorable action on the merits is earnestly solicited at present.

***Claim Rejection under 35 U.S.C. §103(a)***

Claims 10-12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Harada et al.** (JP 2001-172274, English translation) in view of **Hudson, Jr. et al.** (Journal of the American Chemical Society, 1941, Vol. 63, pp. 3163-3164).

Reconsideration and withdraw of the above rejection is respectfully requested based on the following considerations.

***Legal Standard for Determining Prima Facie Obviousness***

M.P.E.P. § 2141 sets forth the guidelines in determining obviousness. First, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), which has provided the controlling framework for an obviousness analysis. The four *Graham* factors are:

- (a) determining the scope and content of the prior art;
- (b) ascertaining the differences between the prior art and the claims in issue;
- (c) resolving the level of ordinary skill in the pertinent art; and
- (d) evaluating any evidence of secondary considerations.

*Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966).

Second, the Examiner has to provide some rationale for determining obviousness. MPEP § 2143 sets forth some rationales that were established in the recent decision of *KSR*

*International Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). Exemplary rationales that may support a conclusion of obviousness include:

- (a) *combining prior art elements according to known methods to yield predictable results;*
- (b) *simple substitution of one known element for another to obtain predictable results;*
- (c) *use of known technique to improve similar devices (methods, or products) in the same way;*
- (d) *applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;*
- (e) *“obvious to try” – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success*
- (f) *known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;*
- (g) *some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.*

As the M.P.E.P. directs, all claim limitations must be considered in view of the cited prior art in order to establish a *prima facie* case of obviousness. See M.P.E.P. § 2143.03.

*Distinctions over the Cited Art*

One of the most important characteristic features of the present invention resides in reacting the substrate (a starting compound) under mild conditions in the presence of an acid.

**Harada et al.** discloses the production of 4-acetyltetrahydropyran by reacting 4-acetyl-4-alkoxycarbonyltetrahydropyran with hydrogen peroxide in the presence of a base as stated on page 2 of the Office Action by the Examiner.

This reference is quite different from the present invention in the point of using a base in place of an acid of the present invention. This is a remarkable difference between the present invention and **Harada et al.**, since the reaction mechanisms would be markedly different in alkaline conditions and acidic conditions.

**Hudson, Jr. et al.** discloses that hydrolyses were effected by boiling the esters with the acetic-sulfuric acid mixtures in a flask connected by a ground-glass joint to a reflux condenser equipped with a bubble counter (see page 3163, right column, lines 6-10 under the chemical formula). In this reference, not only mineral acid (sulfuric acid) but also organic acid (acetic acid) were used. The reason to use the organic acid (acetic acid) in this reference is considered to elevate solubility of the esters.

Since **Harada et al.** uses a base in the reaction and **Hudson, Jr. et al.** uses an acid in the same, it is submitted that there is no motivation provided to those of ordinary skill in the art to combine these two references in the manner being asserted by the USPTO.

In addition, in the present invention, an acid used in the reaction is a mineral acid alone such as an aqueous sulfuric acid alone as described in **Example 1** on page 13, line 22 of the present specification (*see below*) and no organic acid such as acetic acid is used.

[0047]

Example 1 (Synthesis of 4-acetyltetrahydropyran)

In a flask made of glass having an inner volume of 10 ml and equipped with a stirring device, a thermometer and a reflux condenser were charged 0.38 g

(2.0 mmol) of 4-acetyl-4-methoxycarbonyltetrahydropyran with a purity of 99% and synthesized in the same manner as in Reference example 1 and 1.08 ml (10 mmol) of 9 mol/l sulfuric acid, and the mixture was reacted at 120°C for 1.5 hours with stirring. After completion of the reaction, when the reaction mixture was analyzed by gas chromatography (Internal standard method), 0.25 g (Reaction yield: 96%) of 4-acetyltetrahydropyran was found to be formed.

Moreover, in the present invention, a reaction solvent is simpler than those of **Hudson, Jr. et al.**, so that a post-treatment step is also simpler and easier in the present invention. That is, in **Hudson, Jr. et al.**, it is necessary to carry out a treatment for removing the sulfuric acid and acetic acid as the post-treatment step, so that the steps become more complicated (increase in wastes), but in the present invention, the post-treatment can be carried out with a simpler and easier operation.

In the present invention, the reaction of a reactant and an aqueous mineral acid solution such as an aqueous sulfuric acid solution, etc., proceeds at an interface there between, and the product does not mix with the aqueous mineral acid solution such as an aqueous sulfuric acid solution, etc., so that a separation step is easy.

Furthermore, the substituent R at the  $\beta$ -position of the " $\beta$ -keto ester compound" to be used in **Hudson, Jr. et al.**, are all alkyl groups or phenyl groups (as can be seen from the descriptions of " $\beta$ -keto ester used" shown at the left end column of Table 1 on page 3163 of the reference), and they do not contain a cyclic ether group as in the present invention.

Notably, the pyran compound of the present invention is a cyclic ether compound, and such a cyclic ether compound has been known to cause cleavage of the ring under the acidic conditions. For example, the following three (3) literatures have been known and support this

fact. *(The following three (3) literatures are being submitted to the USPTO in an IDS filed concurrently on even day herewith.)*

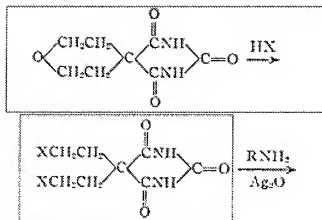
Literature 1: *Helv Chim Acta* .26, pp.1132-1143, 1943 (German-language)

In this literature, 4-aminotetrahydropyran is treated with conc. hydrochloric acid to open the pyran ring. ("5 g of raw 4-Aminotetrahydropyran hydrochloride and 70 cm<sup>3</sup> of conc. hydrochloric acid were heated in an inclusion pipe for 24 hours at 120-130°." as mentioned on page 1134, lines 10-12 thereof (*reproduced below*)).

1,5-Diehler-3-amino-pentan, 5 g rohes 4-Amino-tetrahydro-pyran-hydrochlorid und 70 cm<sup>3</sup> konz. Salzsäure (1,19) wurden im Einschliessrohr 24 Stunden auf 120-130° erhitzt. Der Rohrinhalt wurde mit Wasser verdünnt, mit Tierkohle entfärbt und im Vakuum zur Trockne eingedampft. Es wurden 6,0 g (81 % der Theorie) des kristallinen Hydrochlorids erhalten. Aus Essigester umkristallisiert bildete es viereckige Blättchen, Smp. 180-181°.

Literature 2: *J.A.C.S.*, 81, 1959, pp.5167-5171

A pyran compound (spirotetrahydropyran-4',5-barbituric acid) is treated with KI, phosphoric acid and phosphorus pentoxide to open the pyran ring to form 5,5-bis-(2-iodoethyl)-barbituric acid (see page 5108, left column, the chemical formulae surrounded by a box line and page 5170, the description surrounded by a box line (*each reproduced below*)).



5,5-Bis-(2-iodoethyl)-barbituric Acid.—A mixture of 200 g. of 90% phosphoric acid (prepared from 83% acid and phosphorus pentoxide), 100 g. of potassium iodide and 43.2 g. of spiro-tetrahydropyran-4',5'-barbituric acid (monohydrate) was shaken vigorously for 10 hours at a temperature of 135°. While warm, the resulting dark solution was poured onto 400 g. of crushed ice and the yellow solid which separated was removed by filtering and washed well with cold water. The yield of crude material which melted at

205–208° was 75% of theoretical. Washing with hot (60°) water removed the unreacted starting material from the product and recrystallization from a dioxane-water mixture gave the pure product, melting with decomposition at 207–208°.

Anal. Calcd. for  $C_5H_{10}N_2O_5I_2$ : C, 22.04; H, 2.27; N, 6.44; I, 58.2. Found: C, 22.05; H, 2.31; N, 6.42; I, 58.0.

Literature 3: J.C.S., 1951, pp.2848-2851

A pyran compound (fluorine-9-spiro-4'-tetrahydropyran) is treated with KI, phosphoric acid and phosphoric oxide to open the pyran ring to form 9:9-di-2'-iodoethylfluorine (see page 2851, the description surrounded by a box line (*reproduced below*)).

9:9-Di-2'-iodoethylfluorene.—Fluorene-9-spiro-4'-tetrahydropyran (1.3 g.) was added to potassium iodide (17.6 g.), 80% phosphoric acid (7.2 mL), and phosphoric oxide (3.5 g.). The mixture was heated for 3 hours in an oil-bath, with stirring, under reflux, the temperature being raised from 80° to 130°, and kept at 95–100° for approx. 1½ hours. The cooled mixture was diluted with water and extracted with ether. The ethereal layer was decolorised with sodium thiosulphate solution, washed with sodium chloride solution and water, and dried ( $MgSO_4$ ). On evaporation of the ethereal solution, an oil remained which was dissolved in benzene and chromatographed through alumina (8" × ½") which was eluted with benzene. Unchanged spiran was retained more strongly than was the iodo-compound, giving a fairly sharp separation. Final traces of the spiran were washed from the column with chloroform. 1.58 g. of iodo-compound (m. p. 174–178°) were obtained and 0.31 g. of unchanged starting material. The 9:9-di-2'-iodoethylfluorene, on recrystallisation from light petroleum (b. p. 80–100°), had m. p. 181.5–182° (prisms) (Found: C, 42.7; H, 3.4; I, 53.3%;  $M$ , 479.  $C_{17}H_{14}I_2$  requires C, 43.0; H, 3.4; I, 53.6%;  $M$ , 474).

Thus, those skilled in the art do not generally consider using an acid such as sulfuric acid, etc., on a compound having a pyran structure. However, the present inventors have carried out earnest studies and firstly succeeded in that, in the compound having a pyran structure of the

present invention, an aimed for product can be obtained in an aqueous acidic solution without cleaving the pyran structure.

The Applicant submits that the above-mentioned fact, which could in no way be expected from the references being cited by the USPTO, clearly supports the non-obviousness of the instantly elected invention over the cited art being applied by the USPTO. As such, the USPTO is respectfully requested to withdraw the outstanding rejection over the cited art of record.

### **Conclusion**

Based upon the amendments and remarks presented herein, the Examiner is respectfully requested to issue a Notice of Allowance clearly indicating that each of the pending claims 10-12 and 16-25 is allowable under the provisions of Title 35 of the United States Code.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact John W. Bailey, Reg. No. 32,881 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.



If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

Dated: December 28, 2009

Respectfully submitted,

By 

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